Antibiotic-loaded bone cement (ALBC) is associated with a lower risk of revision following primary cemented total knee replacement (TKR): An analysis of 731,214 cases using National Joint Registry data

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Abstract

Aims

Antibiotic-loaded bone cements (ALBCs) may offer early protection against the formation of bacterial biofilm after joint replacement. Use in hip replacement is widely accepted, but there is a lack of evidence in total knee replacement (TKR). ALBCs are more costly than plain cement, and there are concerns regarding mechanically stability and increased antibiotic resistance. The objective of this study is to evaluate the use of ALBC in a large population of TKR patients in order to give a recommendation about its use based on a risk-benefit profile.

Patients and Methods:

Data from the National Joint Registry (NJR) of England and Wales was obtained for all primary cemented TKRs between March 2003 and July 2016. Patient, implant and surgical variables were analysed. Cox proportional hazards models were used to assess the influence of ALBC on risk of revision. Body mass index (BMI) data was available in a subset of patients.

Results:

Of 731,214 TKRs, 15,295 (2.1%) were implanted with plain and 715,919 (97.9%) with ALBC. There were 13,391 revisions; 2391 were performed for infection. After adjusting for other variables, ALBC had a significantly lower risk of revision for any cause (Hazard Ratio [HR] 0.85, 95% Confidence Intervals [CIs]

0.77-0.93, p<0.01). ALBC was associated with a lower risk of revision for all aseptic causes (HR 0.85, 0.77-0.95, p<0.01) and revisions for infection (HR 0.84, 0.67-1.01, p=0.06). The results were similar when BMI was added into the model (432,003 TKRs, all cause revision HR 0.76, 0.65-0.89, p<0.01, aseptic revisions HR 0.81, 0.67-0.98, p=0.03, revision for infection HR 0.65, 0.49-0.87, p<0.01).

Prosthesis survival at 10 years for TKRs implanted with ALBC was 96.3% [95% CIs 96.3-96.4] compared with 95.5% [95.0-95.9] in those implanted with plain cement. On a population level, where 100,000 TKRs are performed annually, this is equivalent to 870 fewer revisions at 10 years if ALBC was used.

Conclusions:

After adjusting for a range of variables, ALBC was associated with a significantly lower risk of revision. Using ALBC does not increase mid-term implant failure rates. Surgeons using plain cement for primary TKRs should consider changing to ALBC in order to reduce overall revision risk.

Take home message:

- ALBC was associated with a significantly lower risk of revision following primary TKR
- The risk reduction in this analysis would result in 8 fewer revisions at 10 years per 1000 TKRs if ALBC was used rather than plain cement
- Concerns regarding mechanical instability and antibiotic resistance resulting in earlier implant failure when using ALBC are unfounded

Introduction:

Prosthetic infection after total knee replacement (TKR) is a rare but potentially debilitating surgical complication. Its rate has been estimated to be between 1% and 2% [1-3]. Biofilm protects infecting organisms against the host immune system and systemic antibiotics [4,5], and patients with infected TKRs frequently require revision surgery [6], which in turn leads to poorer patient outcome, longer hospitalization and significantly increased cost [2,7].

Adding antibiotics to the cement used in prosthetic joint arthroplasty has been advocated for many years as a means of reducing the risk of infection as well as in the treatment of infected prostheses [8-12]. While the efficacy of antibiotic-loaded bone cement (ALBC) has been demonstrated in revision surgery for both treating prosthetic infection and as prophylaxis [10,11,13], the evidence of its efficacy in primary prophylaxis lacks clarity [7,8,14], and has led to different practices globally [15].

There are also concerns that adding antibiotics to bone cement can adversely affect its mechanical properties [16-19] which would effect revision rates. Some authors also believe this can potentially lead to the development of resistant organisms that may complicate infection management should the prosthetic joint become infected [4,20-23] (although one large study has recently shown local antibiotics in cement does not drive resistant infections [24]). Moreover, there are reports of bone cellular [25,26] and renal toxicity [27-29]. These concerns and uncertainties challenge the practice of routinely adding antibiotics to the cement

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in primary TKR without having strong evidence of its efficacy in reducing the risk of infection.

In this study we sought to evaluate the hypothesis that ALBC reduces the risk of revision following primary TKR. National Joint Registry (NJR) data were analysed to compare the revision rate of primary TKRs performed for osteoarthritis using ALBC versus plain cement, in order to provide informed recommendations about its efficacy and the risk-benefit ratio.

Methods:

A proposal was submitted to the research committee of the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man in 2016. Approval and data access was granted in February 2017. Data were obtained for all primary cemented TKRs recorded on the NJR dataset between 2003 and 2016. Knee replacements that were not fully cemented, unicondylar knee replacements and revision procedures were excluded. Patient, implant and surgical variables collected by the NJR were provided.

A retrospective observational registry study was carried out. The following endpoints (as recorded on the NJR minimum dataset form) were of interest: revision for infection, revision for a cause other than infection, and revision for any cause. The use of ALBC was compared with plain bone cement. For each endpoint, log rank tests and Cox proportional hazards models were performed to compare the groups, both unadjusted for cement variables, and adjusted by stratification for patient (gender, patient age group, ASA Grade, BMI where

available and indication), surgical (approach, surgeon grade, thromoprophylaxis) and implant (constraint, bearing, patella) characteristics. The influence of timing of surgery (i.e. year of operation) was also explored in order to assess the influence of time dependent unknown variables (for e.g. different generations of cementation techniques). Body mass index (BMI) data was not universally collected in the earlier years of the registry, so this data was only available in a subset of patients. Data on some factors that may influence risk of infection, such as immunosuppressing conditions and medications, and smoking, are not collected by the NJR and were therefore unavailable for this analysis.

The statistical models were tested to ensure the proportional hazards assumption was not violated for any of the endpoints ($p < 0.05$). For estimation of the average hazard ratio a weighted Cox regression was performed to calculate an unbiased estimate. Final models were identified by stepwise selection and subjected to robustness checks (including constant proportionality over time). Stratified Cox proportional hazard model was considered to account for year of operations.

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We agreed to use directed acyclic graph for model selection based on the suggestion from NJR, but there was no existing theory or consensus on interrelationships between the covariates. Do we need to include a line or two here to clarify this?

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The analysis was performed on the entire dataset (excluding BMI data) and repeated for episodes with a valid BMI (range of $15 \leq BMI \leq 50$). Frequency and percentages were used to summarise categorical data while mean and standard deviation were used for continuous variables.

The dataset contained 731,214 records. Figures 1 and 2 depict the distribution of the number of patients according to the type of cement used, the surgical outcome (revision or no revision), and whether infection was recorded as the cause for revision. The data was analysed in three ways depending on whether the revised procedure was due to infection or not. In all the analyses, the event was defined as "revision" and censoring was defined when there was no revision procedure as of 31st July 2016.

Table 3 summarises the distribution of patients across all variables in the dataset before and after deleting records with missing BMI data. The American society of anesthesiologist's grade (ASA) variable was recoded into three categories (grade 1, grade 2 and grade ≥ 3). Similarly, age was also recoded into 4 categories using quartiles as cut-points.

Five-year and 10-year survival rates were calculated, with 95% confidence intervals. The data was analysed using SAS 9.4 and R 3.4.0.

Results

Analyses of all patients (excluding BMI data)

Survival curves comparing TKRs performed using ALBC and plain cement show a lower revision rates at two years following surgery in the ALBC group (for the endpoints: all cause revision, revision for infection, revision for aseptic causes), although the statistical significance was marginal where infection was cited as the cause of revision (p=0.06) (Figure 3).

Table 2 presents the univariable analysis. The following factors were independently associated with a significantly increased risk of revision: male sex, younger age, lower ASA, indications other than osteoarthritis, patella unresurfaced, employing posterior stabilised components and mobile bearings, the use of low viscosity and plain (non-antibiotic loaded) cement, and when a factor Xa inhibitor was used for venous thromboembolic (VTE) prophylaxis. There was no evidence of significant association between the hazard of revision and other types of VTE prophylaxis used. Figure 4 shows that changes in rates of revision (hazard ratio) did not vary in a linear manner over time, irrespective of indication. Hazards of revision between the two groups varied across the operation years. In general, plain cement had higher hazard of revision than ALBC, particularly after 2007.

Table 3 presents multivariable analyses for the association between hazard of revision and ALBC status while adjusting for other important factors. In all the analyses, the hazard of revision was about 15% less likely for ALBC than plain cement after adjusting for other factors including the year of operation.

Analyses of episodes with BMI data

There were 432003 records with BMI data. The Kaplan-Meier curves show similar pattern to the analysis with all patients. ALBC had a lower risk of revision than plain cement (Figure 5).

Table 4 shows similar results as the analyses of all patients presented in Table 2. The following factors were independently associated with a significantly increased risk of revision: male sex, younger age, lower ASA, higher BMI, patella unresurfaced, employing posterior stabilised components and mobile bearings, the use of plain (non-antibiotic loaded) cement, and when a factor Xa inhibitor was used for venous thromboembolic (VTE) prophylaxis. Cement viscosity and indication were not associated with revision risk.

Multivariable analysis of the data excluding patients with missing BMI data are presented in Table 5. There is significant association between the hazard of revision and ALBC usage. ALBC has about 15% less chance of revision than non-ALBC, which is similar to the results from the analysis of all patients without adjusting for BMI.

Summary

TKRs implanted with ALBC had a 5-year revision rate of 2.34% (95% CIs 2.30 to 2.39) and a 10-year rate of 3.66% (3.59 to 3.75) compared with 3.02% (2.72 to 3.34) and 4.53% (4.10 to 4.99) when plain cement was employed, after adjusting

for patient and surgical variables. This equates to an absolute 10-year revision risk reduction of 0.87% and a relative risk reduction of 19.2% when ALBC was used. The number of patients needed to treat in one year with ALBC to prevent one revision is 115. On a population level, where 100,000 TKRs are performed annually, this is equivalent to 870 fewer revisions at 10 years if ALBC was used.

Discussion:

This retrospective cohort study provides the largest analysis of ALBC in primary knee replacement patients. All cause revision, revision for aseptic causes and revision where infection was cited as a cause were all significantly lower in the ALBC group compared with plain cement. Crucially, revision risk for aseptic causes was significantly lower when ALBC was used. Concerns regarding greater mechanical instability with the use of ALBC are therefore unfounded in this population-based mid-term study.

However, there are limitations. Data on proven risk factors for periprosthetic joint infection, such as diabetes, smoking and length of surgery [30] were unavailable in this study. ASA grade, whilst crude, was therefore used as a surrogate for comorbidity in statistical models. BMI (which is known to influence risk of infection) data is incomplete within the NJR, although rates of collection have improved in recent years. Despite this, our analyses demonstrated little difference between the cohort with BMI data and the full dataset, when BMI was excluded from the statistical models – ALBC was associated with a significant reduction in revisions, irrespective of BMI.

Registries rely on data collection at time of surgery, resulting in some inaccuracies in stated reason for revision. For example, revisions apportioned to aseptic loosening may ultimately be driven by low-grade infection. As linked microbiological data is unavailable, registry analyses are likely to under report infection as a cause of revision. Moreover, the NJR does not record any information on superficial infections that are treated conservatively and (in the

Commented [s5]: Risk factors associated with revision for prosthetic joint infection after hip replacement: a prospective observational cohort study. Lenguerrand E, Whitehouse MR, Beswick AD, Kunutsor SK, Burston B, Porter M, Blom AW. Lancet Infect Dis. 2018 Sep;18(9):1004-1014. doi: 10.1016/S1473-3099(18)30345-1

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time period of this study) did not record cases of infection where the treatment was a debridement, antibiotics and implant retention (DAIR). However, there would be no logical reason why the use of one type of cement may be more associated with registry process issues than the comparator.

While we were able to identify an association between ALBC and lower infection risk, we lacked detailed information on the type and dosage of the antibiotics added to the cement, antibiotic prophylaxis used and treatment duration, and could not, therefore, produce any useful information on whether certain antibiotics are more effective than others. Furthermore, we have no data on antimicrobial resistance profiles in those patients who were revised for infection following original implantation with ALBC.

Finally, the proportion of knee replacements implanted using plain cement in this study was only 2%, and most were implanted in the earlier years of the registry. Nevertheless, this still accounts for over 15,000 cases and differences in revision rates between cement types were significant despite this relative mismatched group sizes.

Prosthetic joint infection is a serious complication following TKA and frequently requires revision surgery and leads to poor patient outcome and increased cost [2,7]. Antibiotic-loaded bone cement (ALBC) has been used for prophylaxis purposes in primary and revision TKA and also as part of the treatment in revision surgery for infected TKA [8-11]. It is the most frequently used local antibiotic delivery system in joint arthroplasty [31]. Acting as a carrier for topical

delivery of antibiotics, ALBC is thought to reduce the risk of prosthetic infection not addressed by systemic antibiotics due to impaired blood supply, and therefore low local antibiotic concentrations at the surgical site in the immediate postoperative period [14,32].

There is strong evidence of ALBC's efficacy in treating prosthetic TKA infection and as a means of prophylaxis in revision knee surgery. However, its efficacy in providing prophylaxis in primary TKA has been a matter of debate. In fact, the current evidence is so conflicting that while in some studies ALBC was found to reduce the risk of primary TKA infection [13,14,33-40], other studies have shown no difference [41-50] or even increased risk of primary TKA infection because of ALBC [51,52]. We are aware of four recent joint replacement registry-based studies that examined this subject. Namba et al in their study of an American total joint registry identified the use of ALBC in primary TKA as a risk factor for causing deep surgical site infection, but at the same time the authors found that adding antibiotics to the irrigation solution was protective against deep surgical site infection [52]. Tayton et al also found ALBC increased the risk of revision for infection at 6 months in their review of over 60,000 primary knee replacements on the New Zealand joint registry [51]. The use of laminar flow and surgical helmuts was also associated with greater infection risk. However, a significant limitation to their study was that they did not take into account revisions performed after 1 year from the primary operation [51]. In both the American and New Zealand registry studies the authors proposed an explanation for this: the observed paradoxical increase in the rate of infection with the use of ALBC could be a result of selection bias, as ALBC was not routinely used in their countries

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and potentially was selectively used in patients who were identified by the surgeons to have high risk factors for infection. On the contrary, in Finland where ALBC is routinely used in primary TKR, Jamsen et al, in their analysis of the Finnish arthroplasty register found the risk of infection was 1.3x greater when plain cement was used in primary TKR, and this increased to 2.1x in revision TKR [13]. Bohm et al analysed the Canadian joint replacement registry comparing the revision rates (at 2 year follow up) of primary TKR performed using ALBC and plain cement and found no statistically significant difference in the rate of revision for all causes. Interestingly a statistically significant doubling of the rate of revision for aseptic loosening was found in the plain cement group [44]. However, limitations included selection bias (as ALBC may have been used in higher risk patients), and inclusion bias (infections treated with washout and implant retention were not included) [44]. In their systematic review and meta-analysis of randomized controlled trials that investigated the efficacy of ALBC in reducing infection in primary TKA and THA, Wang et al concluded that compared to plain bone cement and the use of systemic antibiotics alone, ALBC effectively reduced the rate of deep wound infection in THA and TKA patients [14]. In the UK, ALBC is routinely used in primary TKA, and we found that it was associated with an overall 15% reduction in the rate of revision for all causes in primary TKA, although the statistical significance was only marginal when we used the revision for infection as the endpoint ($p=0.06$). This decrease in the rate of revision for all causes, more clearly than the rate of revision for infection may be due to subclinical infections that were not detected and were diagnosed and recorded as aseptic loosening or revision for other non-infection causes. This was theorized to have been the case in Bohm et al.'s study where ALBC was

found to reduce the revision rate for aseptic loosening rather than that for infection [44], and in Havelin et al.'s study on hip replacements from the Norwegian arthroplasty register, where the authors found a trend toward lower revision rate due to aseptic loosening in the hip replacements performed using ALBC cement compared to those performed using plain [53].

Several patient characteristics, comorbidities, hospital- and surgeon-related characteristics have been identified in previous arthroplasty registry-based studies as risk factors for developing prosthetic infection after primary TKR. These risk factors are: male sex [3,13,52,54], background of diabetes mellitus [52,55], primary TKR indication being rheumatoid arthritis [13,56], osteonecrosis [52] or post-traumatic arthritis [13,52], high body mass index (BMI) [13,51,52,54], increased ASA score [3,52,57], high volume hospitals [52,58], quadriceps release exposure [52], constrained and hinged knee prostheses [13], and long operative time [3,52,57].
The use of ALBC has been shown to be effective at reducing the rate of infection following primary TKR performed in diabetic patients [40], in patients whose indication for TKR was rheumatoid arthritis [38], and where the primary TKR was performed without "clean-air" measures [35,37].

One of the concerns regarding the use of ALBC for infection prophylaxis in primary joint arthroplasty is the potential for the ALBC to develop resistant organisms that may further complicate infection management should the implant become infected [4,20-23]; or complicate the reliability of joint fluid and tissue cultures during revision surgery [59,60]. However, in a study by Hansen et al. of primary TKAs and THAs performed using ALBC versus plain cement in the

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Commented [AA10]: I checked and both cited papers confirm. In Namba's paper they found that hospitals with higher volume had a statistically significant higher infection rate compared to low volume ones (they grouped the hospitals as >200 cases / year, 100-200 / year and < 100 / year, so all may seem as low volume in UK standard).
The second paper (Kurz) found that urban non-teaching hospitals had a higher infection rate than both rural hospitals and urban teaching hospitals, and then the urban teaching hospitals had a higher infection rate compared to rural hospitals

United States, the authors found no change in the patterns of the infecting organisms, and no notable increase in the percentage resistance of the organisms found at revision surgery [61]. They concluded that the routine prophylactic use of ALBC did not lead to a change in the profile of the infecting pathogen and did not lead to increased resistance of the infecting organisms. Tyas et al. studied the rate of deep surgical site infection in hip hemiarthroplasty performed using high-dose dual-antibiotic cement and those performed using low-dose single-antibiotic cement and while they found a significantly lower rate of infection in patients who received the high-dose dual-antibiotic cement, they too found no increase in the cases of bacterial resistance to antibiotics in the high-dose dual-antibiotic cement group [24].

Another concern is that adding antibiotics to bone cement can adversely affect its mechanical properties [16-19]. However, none of the available arthroplasty registry-based studies found evidence of adverse effect of ALBC on the revision rate for non-infective causes. In contrast, Bohm et al. found that ALBC actually improved the revision rate for aseptic loosening in primary TKAs [44]; and Havelin et al. found a trend toward higher revision rate for aseptic loosening in the hip replacements performed using plain cement rather than those performed using ALBC [53]. We accept that these studies report short-term results and did not assess the longer-term effect. Several studies have also reported incidents of bone cellular [25,26] and renal toxicity [27-29] with ALBC.

A recent cost-effectiveness analysis estimated that a reduction of TKR infection rate by at least 1.2% as a result of ALBC is required to recover the cost and

therefore justify of the routine use of ALBC in TKA [15]. In this current study of NJR data there was an overall reduction in revision risk at 10 years of 0.87%. The NJR annual reports states that 75% of patients with TKR are alive at 10 years following surgery.[62] It is therefore entirely feasible that risk reduction over the lifetime of these implants may exceed this cost-effectiveness threshold of 1.2%.

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Conclusions

After adjusting for a range of variables, ALBC was associated with a 19% lower risk of revision. Using ALBC does not increase mid-term implant failure rates. Surgeons using plain cement for primary TKRs should consider changing to ALBC in order to reduce overall revision risk.

We thank the patients and staff of all the hospitals in England, Wales and Northern Ireland who have contributed data to the National Joint Registry. We are grateful to the Healthcare Quality Improvement Partnership (HQIP), the NJR Research Sub-committee and staff at the NJR Centre for facilitating this work. The authors have conformed to the NJR's standard protocol for data access and publication. The views expressed represent those of the authors and do not necessarily reflect those of the National Joint Registry Steering Committee or the Health Quality Improvement Partnership (HQIP) who do not vouch for how the information is presented.

References

1. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med* 2004;351-16:1645-54.

2. Garvin KL, Konigsberg BS. Infection following total knee arthroplasty: prevention and management. *J Bone Joint Surg Am* 2011;93-12:1167-75.

3. Kurtz SM, Ong KL, Lau E, Bozic KJ, Berry D, Parvizi J. Prosthetic joint infection risk after TKA in the Medicare population. *Clin Orthop Relat Res* 2010;468-1:52-6.

4. van de Belt H, Neut D, Schenk W, van Horn JR, van Der Mei HC, Busscher HJ. Staphylococcus aureus biofilm formation on different gentamicin-loaded polymethylmethacrylate bone cements. *Biomaterials* 2001;22-12:1607-11.

5. Gristina AG, Costerton JW. Bacterial adherence to biomaterials and tissue. The significance of its role in clinical sepsis. *J Bone Joint Surg Am* 1985;67-2:264-73.

6. Grammatopoulos G, Bolduc ME, Atkins BL, Kendrick BJL, McLardy-Smith P, Murray DW, Gundle R, Taylor AH. Functional outcome of debridement, antibiotics and implant retention in periprosthetic joint infection involving the hip: a case-control study. *Bone Joint J* 2017;99-B-5:614-22.

7. (CADTH) CAfDaTiH. Antibiotic Impregnated Cement for Primary Hip or Knee Arthroplasty: A Review of the Clinical and Cost-Effectiveness. In. Ottawa (ON), 2015.

8. Hinarejos P, Guirro P, Puig-Verdie L, Torres-Claramunt R, Leal-Blanquet J, Sanchez-Soler J, Monllau JC. Use of antibiotic-loaded cement in total knee arthroplasty. *World J Orthop* 2015;6-11:877-85.

9. Buchholz HW, Engelbrecht H. [Depot effects of various antibiotics mixed with Palacos resins]. *Chirurg* 1970;41-11:511-5.

10. Bourne RB. Prophylactic use of antibiotic bone cement: an emerging standard--in the affirmative. *J Arthroplasty* 2004;19-4 Suppl 1:69-72.

11. Hanssen AD. Prophylactic use of antibiotic bone cement: an emerging standard--in opposition. *J Arthroplasty* 2004;19-4 Suppl 1:73-7.

12. Sprowson AP, Jensen C, Chambers S, Parsons NR, Aradhyula NM, Carluke I, Inman D, Reed MR. The use of high-dose dual-impregnated antibiotic-laden cement with hemiarthroplasty for the treatment of a fracture of the hip: The Fractured Hip Infection trial. *Bone Joint J* 2016;98-B-11:1534-41.

13. Jamsen E, Huhtala H, Puolakka T, Moilanen T. Risk factors for infection after knee arthroplasty. A register-based analysis of 43,149 cases. *J Bone Joint Surg Am* 2009;91-1:38-47.

14. Wang J, Zhu C, Cheng T, Peng X, Zhang W, Qin H, Zhang X. A systematic review and meta-analysis of antibiotic-impregnated bone cement use in primary total hip or knee arthroplasty. *PLoS One* 2013;8-12:e82745.

15. Randelli P, Evola FR, Cabitza P, Polli L, Denti M, Vaienti L. Prophylactic use of antibiotic-loaded bone cement in primary total knee replacement. *Knee Surg Sports Traumatol Arthrosc* 2010;18-2:181-6.

16. Lautenschlager EP, Jacobs JJ, Marshall GW, Meyer PR, Jr. Mechanical properties of bone cements containing large doses of antibiotic powders. *J Biomed Mater Res* 1976;10-6:929-38.

17. Bistolfi A, Massazza G, Verne E, Masse A, Deledda D, Ferraris S, Miola M, Galetto F, Crova M. Antibiotic-loaded cement in orthopedic surgery: a review. *ISRN Orthop* 2011;2011:290851.

18. Klekamp J, Dawson JM, Haas DW, DeBoer D, Christie M. The use of vancomycin and tobramycin in acrylic bone cement: biomechanical effects and elution kinetics for use in joint arthroplasty. *J Arthroplasty* 1999;14-3:339-46.

19. Dunne NJ, Hill J, McAfee P, Kirkpatrick R, Patrick S, Tunney M. Incorporation of large amounts of gentamicin sulphate into acrylic bone cement: effect on handling and mechanical properties, antibiotic release, and biofilm formation. *Proc Inst Mech Eng H* 2008;222-3:355-65.

20. Neut D, van de Belt H, Stokroos I, van Horn JR, van der Mei HC, Busscher HJ. Biomaterial-associated infection of gentamicin-loaded PMMA beads in orthopaedic revision surgery. *J Antimicrob Chemother* 2001;47-6:885-91.

21. Hendriks JG, Neut D, van Horn JR, van der Mei HC, Busscher HJ. Bacterial survival in the interfacial gap in gentamicin-loaded acrylic bone cements. *J Bone Joint Surg Br* 2005;87-2:272-6.

22. Corona PS, Espinal L, Rodriguez-Pardo D, Pigrau C, Larrosa N, Flores X. Antibiotic susceptibility in gram-positive chronic joint arthroplasty infections: increased aminoglycoside resistance rate in patients with prior aminoglycoside-impregnated cement spacer use. *J Arthroplasty* 2014;29-8:1617-21.

23. Josefsson G, Kolmert L. Prophylaxis with systematic antibiotics versus gentamicin bone cement in total hip arthroplasty. A ten-year survey of 1,688 hips. *Clin Orthop Relat Res* 1993-292:210-4.

24. Tyas B, Marsh M, Oswald T, Refaie R, Molyneux C, Reed M. Antibiotic resistance profiles of deep surgical site infections in hip hemiarthroplasty; comparing low dose single antibiotic versus high dose dual antibiotic impregnated cement. *J Bone Jt Infect* 2018;3-3:123-9.

25. Edin ML, Miclau T, Lester GE, Lindsey RW, Dahners LE. Effect of cefazolin and vancomycin on osteoblasts in vitro. *Clin Orthop Relat Res* 1996-333:245-51.

26. Ince A, Schutze N, Hendrich C, Jakob F, Eulert J, Lohr JF. Effect of polyhexanide and gentamycin on human osteoblasts and endothelial cells. *Swiss Med Wkly* 2007;137-9-10:139-45.

27. Curtis JM, Sternhagen V, Batts D. Acute renal failure after placement of tobramycin-impregnated bone cement in an infected total knee arthroplasty. *Pharmacotherapy* 2005;25-6:876-80.

28. Dovas S, Liakopoulos V, Papatheodorou L, Chronopoulou I, Papavasiliou V, Atmatzidis E, Giannopoulou M, Eleftheriadis T, Simopoulou T, Karachalios T, Stefanidis I. Acute renal failure after antibiotic-impregnated bone cement treatment of an infected total knee arthroplasty. *Clin Nephrol* 2008;69-3:207-12.

29. van Raaij TM, Visser LE, Vulto AG, Verhaar JA. Acute renal failure after local gentamicin treatment in an infected total knee arthroplasty. *J Arthroplasty* 2002;17-7:948-50.

30. Lenguerrand E, Whitehouse MR, Beswick AD, Kunutsor SK, Burston B, Porter M, Blom AW. Risk factors associated with revision for prosthetic joint infection after hip replacement: a prospective observational cohort study. *Lancet Infect Dis* 2018;18-9:1004-14.

31. Jaeblon T. Polymethylmethacrylate: properties and contemporary uses in orthopaedics. *J Am Acad Orthop Surg* 2010;18-5:297-305.

32. Ueng SW, Hsieh PH, Shih HN, Chan YS, Lee MS, Chang Y. Antibacterial activity of joint fluid in cemented total-knee arthroplasty: an in vivo comparative study of polymethylmethacrylate with and without antibiotic loading. *Antimicrob Agents Chemother* 2012;56-11:5541-6.

33. Gutowski CJ, Zmistowski BM, Clyde CT, Parvizi J. The economics of using prophylactic antibiotic-loaded bone cement in total knee replacement. *Bone Joint J* 2014;96-B-1:65-9.

34. Wu CT, Chen IL, Wang JW, Ko JY, Wang CJ, Lee CH. Surgical Site Infection After Total Knee Arthroplasty: Risk Factors in Patients With Timely Administration of Systemic Prophylactic Antibiotics. *J Arthroplasty* 2016;31-7:1568-73.

35. Gorenoi V, Schonermark MP, Hagen A. Prevention of infection after knee arthroplasty. *GMS Health Technol Assess* 2010;6:Doc10.

36. Dunbar MJ. Antibiotic bone cements: their use in routine primary total joint arthroplasty is justified. *Orthopedics* 2009;32-9.

37. Chiu FY, Chen CM, Lin CF, Lo WH. Cefuroxime-impregnated cement in primary total knee arthroplasty: a prospective, randomized study of three hundred and forty knees. *J Bone Joint Surg Am* 2002;84-A-5:759-62.

38. Liu HT, Chiu FY, Chen CM, Chen TH. The combination of systemic antibiotics and antibiotics impregnated cement in primary total knee arthroplasty in patients of rheumatoid arthritis--evaluation of 60 knees. *J Chin Med Assoc* 2003;66-9:533-6.

39. Eveillard M, Mertl P, Tramier B, Eb F. Effectiveness of gentamicin-impregnated cement in the prevention of deep wound infection after primary total knee arthroplasty. *Infect Control Hosp Epidemiol* 2003;24-10:778-80.

40. Chiu FY, Lin CF, Chen CM, Lo WH, Chaung TY. Cefuroxime-impregnated cement at primary total knee arthroplasty in diabetes mellitus. A prospective, randomised study. *J Bone Joint Surg Br* 2001;83-5:691-5.

41. Wang H, Qiu GX, Lin J, Jin J, Qian WW, Weng XS. Antibiotic Bone Cement Cannot Reduce Deep Infection After Primary Total Knee Arthroplasty. *Orthopedics* 2015;38-6:e462-6.

42. Zhou Y, Li L, Zhou Q, Yuan S, Wu Y, Zhao H, Wu H. Lack of efficacy of prophylactic application of antibiotic-loaded bone cement for prevention of infection in primary total knee arthroplasty: results of a meta-analysis. *Surg Infect (Larchmt)* 2015;16-2:183-7.

43. Qadir R, Sidhu S, Ochsner JL, Meyer MS, Chimento GF. Risk stratified usage of antibiotic-loaded bone cement for primary total knee arthroplasty: short term infection outcomes with a standardized cement protocol. *J Arthroplasty* 2014;29-8:1622-4.

44. Bohm E, Zhu N, Gu J, de Guia N, Linton C, Anderson T, Paton D, Dunbar M. Does adding antibiotics to cement reduce the need for early revision in total knee arthroplasty? *Clin Orthop Relat Res* 2014;472-1:162-8.

45. Hinarejos P, Guirro P, Leal J, Montserrat F, Pelfort X, Sorli ML, Horcajada JP, Puig L. The use of erythromycin and colistin-loaded cement in total knee arthroplasty does not reduce the incidence of infection: a prospective randomized study in 3000 knees. *J Bone Joint Surg Am* 2013;95-9:769-74.

46. Namba RS, Chen Y, Paxton EW, Slipchenko T, Fithian DC. Outcomes of routine use of antibiotic-loaded cement in primary total knee arthroplasty. *J Arthroplasty* 2009;24-6 Suppl:44-7.

47. Gandhi R, Razak F, Pathy R, Davey JR, Syed K, Mahomed NN. Antibiotic bone cement and the incidence of deep infection after total knee arthroplasty. *J Arthroplasty* 2009;24-7:1015-8.

48. Minnema B, Vearncombe M, Augustin A, Gollish J, Simor AE. Risk factors for surgical-site infection following primary total knee arthroplasty. *Infect Control Hosp Epidemiol* 2004;25-6:477-80.

49. McQueen MM, Hughes SP, May P, Verity L. Cefuroxime in total joint arthroplasty. Intravenous or in bone cement. *J Arthroplasty* 1990;5-2:169-72.

50. McQueen M, Littlejohn A, Hughes SP. A comparison of systemic cefuroxime and cefuroxime loaded bone cement in the prevention of early infection after total joint replacement. *Int Orthop* 1987;11-3:241-3.

51. Tayton ER, Frampton C, Hooper GJ, Young SW. The impact of patient and surgical factors on the rate of infection after primary total knee arthroplasty: an analysis of 64,566 joints from the New Zealand Joint Registry. *Bone Joint J* 2016;98-B-3:334-40.

52. Namba RS, Inacio MC, Paxton EW. Risk factors associated with deep surgical site infections after primary total knee arthroplasty: an analysis of 56,216 knees. *J Bone Joint Surg Am* 2013;95-9:775-82.

53. Havelin LI, Espehaug B, Vollset SE, Engesaeter LB. The effect of the type of cement on early revision of Charnley total hip prostheses. A review of eight thousand five hundred and seventy-nine primary arthroplasties from the Norwegian Arthroplasty Register. *J Bone Joint Surg Am* 1995;77-10:1543-50.

54. Malinzak RA, Ritter MA, Berend ME, Meding JB, Olberding EM, Davis KE. Morbidly obese, diabetic, younger, and unilateral joint arthroplasty patients have elevated total joint arthroplasty infection rates. *J Arthroplasty* 2009;24-6 Suppl:84-8.

55. Yang K, Yeo SJ, Lee BP, Lo NN. Total knee arthroplasty in diabetic patients: a study of 109 consecutive cases. *J Arthroplasty* 2001;16-1:102-6.

56. Robertsson O, Knutson K, Lewold S, Lidgren L. The Swedish Knee Arthroplasty Register 1975-1997: an update with special emphasis on 41,223 knees operated on in 1988-1997. *Acta Orthop Scand* 2001;72-5:503-13.

57. Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. *Clin Orthop Relat Res* 2008;466-7:1710-5.

58. Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. *J Arthroplasty* 2008;23-7:984-91.

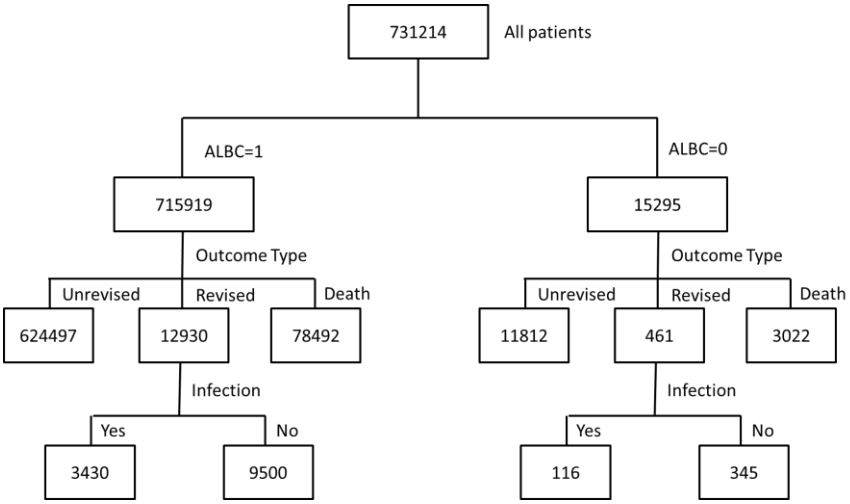
59. Powles JW, Spencer RF, Lovering AM. Gentamicin release from old cement during revision hip arthroplasty. *J Bone Joint Surg Br* 1998;80-4:607-10.

60. Fletcher MD, Spencer RF, Langkamer VG, Lovering AM. Gentamicin concentrations in diagnostic aspirates from 25 patients with hip and knee arthroplasties. *Acta Orthop Scand* 2004;75-2:173-6.

61. Hansen EN, Adeli B, Kenyon R, Parvizi J. Routine use of antibiotic laden bone cement for primary total knee arthroplasty: impact on infecting microbial patterns and resistance profiles. *J Arthroplasty* 2014;29-6:1123-7.

62. NJR. National Joint Registry for England, Wales and Northern Ireland. 15th Annual Report In, 2018.

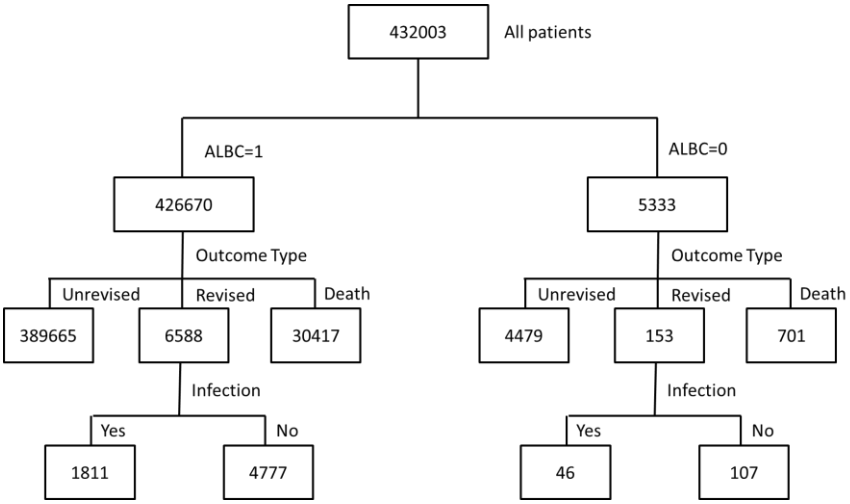
Figure 1: Distribution of number of patients before deleting missing body mass index data



ALBC – antibiotic loaded bone cement

Commented [SJ14]: Change ALBC labels to 'ALBC used' and 'plain cement used'

Figure 2: Distribution of number of patients after deleting missing data (BMI)



BMI – body mass index, ALBC – antibiotic loaded bone cement

Table 1: Characteristics of patients in the dataset

Variable		All data (n=731214)	Data with BMI (n=432003)
Age, mean (sd)		70.2 (9.3)	70.1 (9.3)
Sex, n (%)	Female	422218 (57.7)	248343 (57.5)
	Male	308996 (42.3)	183660 (42.5)
BMI, mean (sd)			30.8 (5.4)
ASA	1	80642 (11.0)	42763 (9.9)
	2	530146 (72.5)	316678 (73.3)
	3	117837 (16.1)	71268 (16.5)
	4	2484 (0.3)	1274 (0.3)
	5	105 (0.0)	20 (0.0)
Indication	Osteoarthritis	710844 (97.2)	421485 (97.6)
	Other	20369 (2.8)	10518 (2.4)
Primary Lead, n	Number	5773	4987
Primary Consultant	Number	2984	2618
Surgical Units	Number	451	431
Surgeon	Consultant	580287 (79.4)	348213 (80.6)
	SAS/Staff	53854 (7.4)	28823 (6.7)
	Registrar/ST	69290 (9.5)	39446 (9.1)
	Other	27783 (3.8)	15521 (3.6)
Approach	Medial parapatellar	681314 (93.2)	403496 (93.4)
	Other	49900 (6.82)	28507 (6.6)
Cement type	ALBC	715919 (97.9)	426670 (98.8)
	Plain	15295 (2.1)	5333 (1.2)
Cement viscosity	High	693867 (94.9)	411335 (95.2)
	Medium	32959 (4.5)	19282 (4.5)
	Low	4388 (0.6)	1386 (0.3)
Bearing	Fixed	602228 (82.4)	359414 (83.2)
	Mobile	36999 (5.1)	18992 (4.4)
	Unknown	91987 (12.6)	53597 (12.4)
Constraint	Unconstrained	446666 (61.1)	269029 (62.3)
	Posterior stabilised	192473 (26.3)	109330 (25.3)
	Other	92075 (12.6)	53644 (12.4)
Patella resurfaced	No	452219 (61.8)	262478 (60.8)
	Yes	278995 (38.16)	169525 (39.2)
Mechanical VTE prophylaxis	No	687661 (94.0)	410771 (95.1)
	Yes	43553 (6.0)	21232 (4.9)
Chemical thrombo-prophylaxis	No	46392 (6.3)	19478 (4.5)
	Yes	684822 (93.7)	412525 (95.5)
Type:			
LMWH	No	229473 (31.4)	131163 (30.4)
	Yes	501741 (68.6)	300840 (69.6)
Aspirin	No	639477 (87.5)	384243 (88.9)
	Yes	91737 (12.6)	47760 (11.1)
Direct Thrombin Inhibitor	No	679648 (93.0)	392831 (90.9)
	Yes	51566 (7.1)	39172 (9.1)

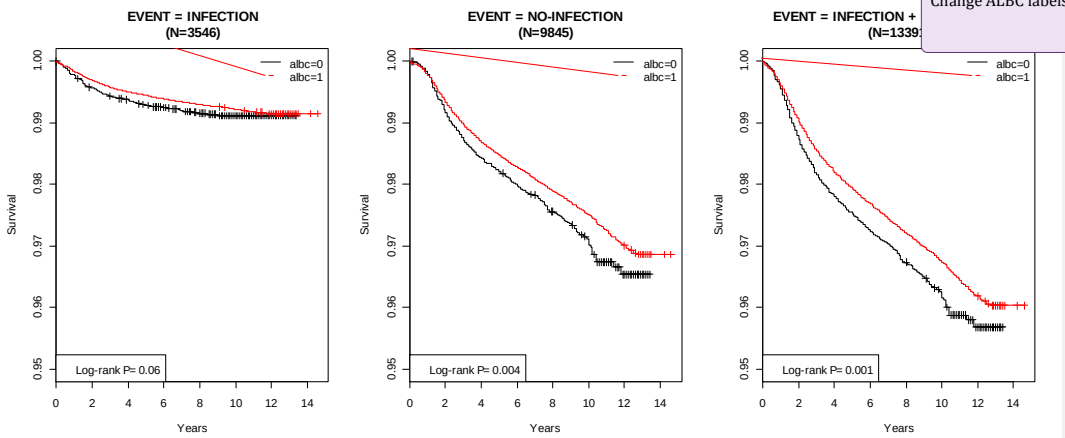
Commented [SJ15]: James suggested separate columns for plain and ALBC
Adetatyo – can this be done?

Variable		All data (n=731214)		Data with BMI (n=432003)	
FactorXa Inhibitor	No	695711	(96.0)	408698	(94.6)
	Yes	28878	(4.0)	23305	(5.4)
Warfarin	No	723337	(98.9)	428006	(99.1)
	Yes	7877	(1.1)	3997	(0.9)
Pentasaccharide	No	724024	(99.0)	427427	(98.9)
	Yes	7190	(1.0)	4576	(1.1)
Other	No	681637	(93.3)	397514	(92.0)
	Yes	48684	(6.7)	34489	(8.0)
Outcome	Revised	13391	(1.8)	6741	(1.6)
	Death	81514	(11.2)	31118	(7.2)
	Unrevised	636309	(87.2)	394144	(91.2)
Revisions:					
Indication	Aseptic	9845	(73.5)	4884	(72.5)
	Infection	3546	(26.5)	1857	(27.6)
Revision Procedure Type	Single stage revision	10246	(76.5)	5202	(77.2)
	Revision 1st stage	2239	(16.7)	1174	(17.4)
	Revision 2nd stage	873	(6.4)	353	(5.2)
	Conversion	26	(0.2)	11	(0.2)
	Amputation	7	(0.1)	1	(0.0)

BMI – body mass index
ASA – American Society of Anesthesiologists
SAS – Staff/Associate Specialist
ST – Specialty trainee
ALBC – Antibiotic loaded bone cement
VTE – Venous thromboembolic
LMWH – Low molecular weight heparin

Figure 3: Survival curves for each revision category, stratified by cement type (n=revision events).

Commented [SJ16]: Remove red line
Change titles of graphs
Change ALBC labels to 'ALBC used' and 'plain cement used'



ALBC – antibiotic loaded bone cement

Figure 4: Line charts describing the association between the hazards of revision and the year of operations for each revision category

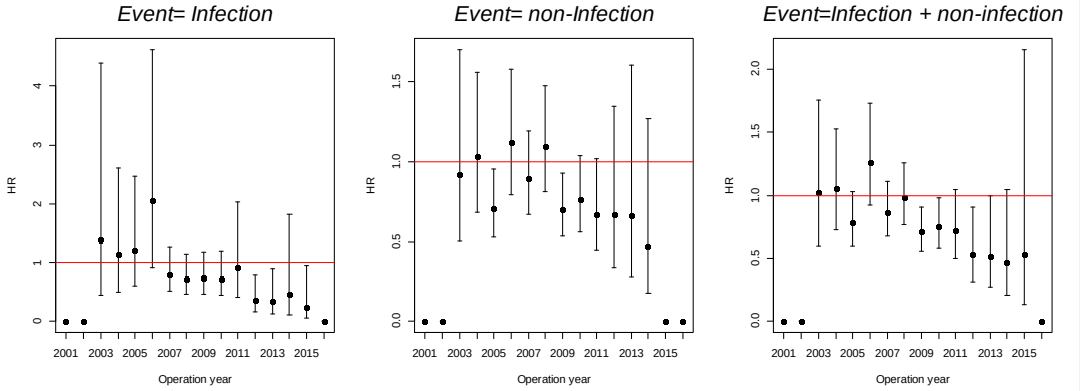


Table 2: Simple (unadjusted) analyses for the three categories of revision groups using the entire dataset. (BMI was not included in these analyses)

	Revision for infection		**Aseptic revision**		**All cause revision**	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age						
<64	Reference					
64-71	0.79 (0.73,0.86)	<0.001	0.60 (0.57,0.63)	<0.001	0.64 (0.62,0.67)	<0.001
71.1-77	0.63 (0.58,0.69)	<0.001	0.41 (0.39,0.44)	<0.001	0.46 (0.44,0.48)	<0.001
>77.1	0.55 (0.50,0.60)	<0.001	0.26 (0.25,0.28)	<0.001	0.33 (0.31,0.34)	<0.001
Sex						
Female	Reference					
Male	1.86 (1.74,1.99)	<0.001	1.02 (0.98,1.06)	0.355	1.19 (1.16,1.24)	<0.001
ASA grade						
1	Reference					
2	1.06 (0.95,1.18)	0.276	0.85 (0.80,0.90)	<0.001	0.89 (0.85,0.94)	<0.001
≥3	1.48 (1.31,1.67)	<0.001	0.79 (0.73,0.85)	<0.001	0.94 (0.88,1.00)	0.037
Indication						
Other	Reference					
Osteoarthritis	0.63 (0.54,0.74)	<0.001	1.05 (0.93,1.19)	0.401	0.90 (0.82,0.99)	0.026
Operation year	1.00 (0.98,1.01)	0.423	1.00 (0.99,1.01)	0.475	1.00 (0.99,1.00)	0.301
Approach						
Other	Reference					
Medial parapatellar	1.06 (0.93,1.21)	0.384	1.00 (0.92,1.08)	0.931	1.01 (0.95,1.08)	0.710
Cement type						
Plain	Reference					
Antibiotic loaded	0.84 (0.67,1.01)	0.061	0.85 (0.77,0.95)	0.004	0.85 (0.77,0.93)	<0.001
Cement viscosity						
High	Reference					
Medium	1.07 (0.92,1.25)	0.363	0.99 (0.90,1.08)	0.768	1.01 (0.93,1.09)	0.833
Low	1.17 (0.84,1.63)	0.362	1.56(1.32,1.83)	<0.001	1.46 (1.26,1.69)	<0.001
Bearing						
Fixed	Reference					
Mobile	1.14 (0.99,1.30)	0.062	1.44 (1.34,1.55)	<0.001	1.36 (1.28,1.45)	<0.001
Unknown	1.03 (0.94,1.13)	0.560	0.99 (0.93,1.04)	0.618	1.00 (0.95,1.05)	0.894
Constraint						
Unconstrained	Reference					
Posterior stabilized	1.31 (1.21,1.41)	<0.001	1.20 (1.14,1.25)	<0.001	1.22 (1.18,1.27)	<0.001
Other	1.12 (1.01,1.23)	0.031	1.02 (0.96,1.08)	0.631	1.04 (0.99,1.10)	0.129
Patellar resurfaced						
No	Reference					
Yes	1.11 (1.03,1.18)	0.003	0.75 (0.72,0.78)	<0.001	0.84 (0.81,0.87)	<0.001
Mechanical VTE thromboprophylaxis						
None	Reference					
Yes	1.07 (0.95,1.22)	0.274	0.99 (0.92,1.07)	0.791	1.01 (0.95,1.08)	0.748
Chemical VTE thromboprophylaxis						
Yes	Reference					
None	0.95 (0.84,1.07)	0.411	0.95 (0.88,1.02)	0.138	0.95 (0.89,1.01)	0.090
Type of chemical VTE thromboprophylaxis:						
Aspirin						
No	Reference					
Yes	1.07 (0.98,1.17)	0.147	0.95 (0.90,1.00)	0.067	0.98 (0.94,1.03)	0.398
LMWH						
No	Reference					
Yes	1.02 (0.95,1.09)	0.590	0.98 (0.94,1.03)	0.452	0.99 (0.96,1.03)	0.713
Pentasaccaride						
No	Reference					
Yes	1.14 (0.84,1.56)	0.393	0.95 (0.77,1.16)	0.610	1.00 (0.84,1.19)	0.995
Warfarin						
No	Reference					

	Revision for infection		Aseptic revision		All cause revision	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Yes	1.02 (0.75,1.39)	0.883	0.80 (0.66,0.99)	0.037	0.86 (0.73,1.02)	0.085
Direct Thrombin Inhibitor						
No	Reference					
Yes	1.04 (0.90,1.20)	0.586	0.95 (0.86,1.04)	0.234	0.97 (0.90,1.05)	0.476
Factor Xa inhibitor						
No	Reference					
Yes	1.02 (0.75,1.39)	0.886	0.52 (0.37,0.74)	<0.001	0.73 (0.58,0.91)	0.007

CI – Confidence intervals
HR – Hazard ratio
ASA – American Society of Anesthesiologists
VTE – Venous thromboembolic
LMWH – Low molecular weight heparin

Table 3: Multivariable (adjusted) analysis of association between revision rate (all cause) and the use ALBC, adjusting for other factors (including year of operation) using un-stratified and stratified Cox proportional hazard models. (Only variable categories with significant influences included here. BMI was not included in these analyses)

	UNSTRATIFIED ANALYSIS				**STRATIFIED ANALYSIS**			
	ALL PATIENTS		**EXCLUDING DEAD**		**ALL PATIENTS**		**EXCLUDING DEAD**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age								
<64	Reference							
64-71	0.64 (0.61,0.67)	<0.001	0.66 (0.64,0.69)	<0.001	0.64 (0.61,0.67)	<0.001	0.66 (0.64,0.69)	<0.001
71.1-77	0.46 (0.44,0.48)	<0.001	0.51 (0.49,0.54)	<0.001	0.46 (0.44,0.48)	<0.001	0.51 (0.49,0.54)	<0.001
>77.1	0.32 (0.30,0.34)	<0.001	0.42 (0.40,0.45)	<0.001	0.32 (0.31,0.34)	<0.001	0.43 (0.41,0.45)	<0.001
Sex								
Female	Reference							
Male	1.15 (1.11,1.19)	<0.001	1.18 (1.14,1.22)	<0.001	1.15 (1.11,1.19)	<0.001	1.19 (1.15,1.23)	<0.001
ASA grade								
1	Reference							
2	1.06 (1.00,1.11)	0.035	1.051 (1,1.105)	0.052	1.05 (1.00,1.10)	0.060	1.08 (1.02,1.13)	0.005
≥3	1.22 (1.14,1.30)	<0.001	1.29 (1.21,1.37)	<0.001	1.21 (1.14,1.29)	<0.001	1.33 (1.25,1.41)	<0.001
Indication								
Other	Reference							
Osteoarthritis	1.04 (0.95,1.14)	0.423	0.99 (0.90,1.09)	0.867	1.04 (0.94,1.14)	0.455	1.00 (0.91,1.10)	0.975
Cement type								
Plain	Reference							
Antibiotic loaded	0.84 (0.77,0.92)	<0.001	0.81 (0.73,0.89)	<0.001	0.85 (0.77,0.93)	<0.001	0.85 (0.77,0.93)	0.001
Cement viscosity								
High	Reference							
Medium	1.04 (0.96,1.13)	0.322	1.05 (0.97,1.14)	0.211	1.04 (0.96,1.13)	0.300	1.05 (0.96,1.13)	0.286
Low	1.61 (1.39,1.86)	<0.001	1.75 (1.51,2.02)	<0.001	1.62 (1.40,1.88)	<0.001	1.62 (1.40,1.88)	<0.001
Bearing								
Fixed	Reference							
Mobile	1.25 (1.17,1.33)	<0.001	1.27 (1.19,1.35)	<0.001	1.24 (1.16,1.32)	<0.001	1.23 (1.15,1.31)	<0.001
Unknown	0.85 (0.27, 2.63)	0.772	0.87 (0.28,2.70)	0.806	0.84 (0.27,2.61)	0.764	0.82 (0.26,2.56)	0.738
Constraint								
Unconstrained	Reference							
Posterior stabilized	1.28 (1.23,1.33)	<0.001	1.29 (1.24,1.34)	<0.001	1.28 (1.23,1.33)	<0.001	1.28 (1.23,1.33)	<0.001
Other	1.30 (0.42,4.05)	0.648	1.29 (0.41,4.00)	0.662	1.30 (0.42,4.04)	0.649	1.33 (0.43,4.12)	0.624
P*atellar resurfaced*								
No	Reference							
Yes	0.81 (0.79,0.84)	<0.001	0.81 (0.78,0.84)	<0.001	0.81 (0.76,0.84)	<0.001	0.82 (0.76,0.85)	<0.001

CI – Confidence intervals
HR – Hazard ratio
ASA – American Society of Anesthesiologists

Figure 5: Survival curves stratified by ALBC when the event is due to infection (left panel), to no-infection (middle panel) and when we combine the infection and no-infection. N represents the number of events, particularly after two years.

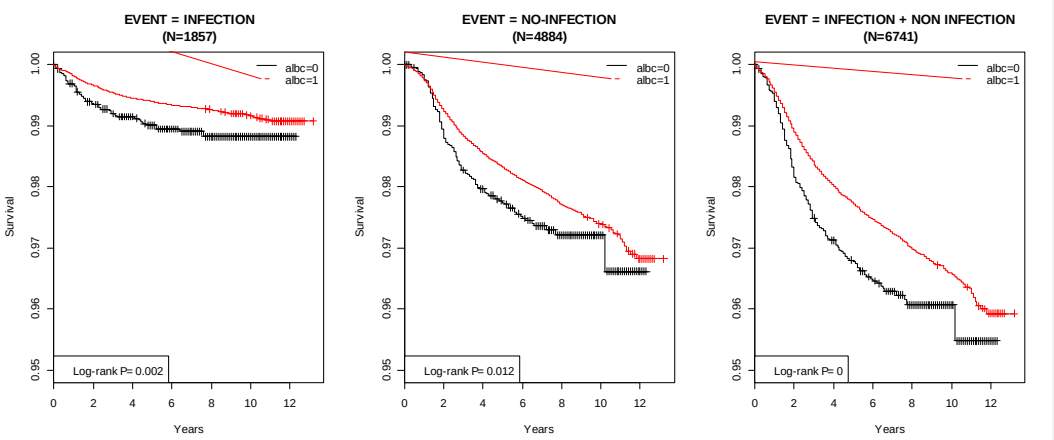


Table 4: Simple (unadjusted) analyses for the three categories of revision groups using the dataset where BMI data was available

	Revision for infection		**Aseptic revision**		**All cause revision**	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age						
<64	Reference					
64-71	0.71 (0.63,0.80)	<0.001	0.57 (0.53,0.61)	<0.001	0.61 (0.57,0.64)	<0.001
71.1-77	0.59 (0.52,0.67)	<0.001	0.43 (0.40,0.47)	<0.001	0.47 (0.44,0.50)	<0.001
>77.1	0.57 (0.50,0.65)	<0.001	0.30 (0.27,0.33)	<0.001	0.37 (0.34,0.39)	<0.001
Sex						
Female	Reference					
Male	1.93 (1.76,2.12)	<0.001	1.01 (0.96,1.07)	0.69	1.21 (1.15,1.27)	<0.001
ASA grade						
1	Reference					
2	1.11 (0.95,1.31)	0.201	0.80 (0.74,0.88)	<0.001	0.87 (0.80,0.93)	<0.001
≥3	1.72 (1.43,2.06)	<0.001	0.77 (0.70,0.86)	<0.001	0.97 (0.88,1.06)	0.468
BMI	1.05 (1.04,1.05)	<0.001	1.02 (1.02,1.03)	<0.001	1.03 (1.03,1.03)	<0.001
Indication						
Other	Reference					
Osteoarthritis	0.59 (0.47,0.75)	<0.001	1.02 (0.85,1.23)	0.808	0.86 (0.74,0.99)	0.031
Operation year	0.98 (0.97,1.00)	0.082	0.98 (0.96,0.99)	<0.001	0.98 (0.97,0.99)	<0.001
Approach						
Other	Reference					
Medial parapatellar	0.99 (0.83,1.19)	0.928	0.96 (0.86,1.07)	0.452	0.97 (0.88,1.06)	0.491
Cement type						
Plain	Reference					
Antibiotic loaded	0.65 (0.49,0.87)	0.004	0.81 (0.67,0.98)	0.029	0.76 (0.65,0.89)	0.001
Cement viscosity						
High	Reference					
Medium	1.12 (0.91,1.38)	0.292	0.95 (0.83,1.09)	0.495	1.00 (0.89,1.12)	0.976
Low	1.13 (0.61,2.11)	0.694	1.06 (0.73,1.54)	0.762	1.08 (0.78,1.48)	0.645
Bearing						
Fixed	Reference					
Mobile	1.14 (0.94,1.39)	0.174	1.42 (1.28,1.58)	<0.001	1.34 (1.23,1.47)	<0.001
Unknown	0.94 (0.82,1.08)	0.385	0.99 (0.91,1.07)	0.750	0.97 (0.91,1.05)	0.466
Constraint						
Unconstrained	Reference					
Posterior stabilized	1.33 (1.20,1.47)	<0.001	1.16 (1.09,1.23)	<0.001	1.20 (1.14,1.27)	<0.001
Other	1.02 (0.89,1.18)	0.744	1.01 (0.93,1.10)	0.835	1.01 (0.94,1.09)	0.723
Patellar resurfaced						
No	Reference					
Yes	1.07 (0.98,1.18)	0.132	0.71 (0.66,0.75)	<0.001	0.80 (0.76,0.84)	<0.001
Mechanical VTE thromboprophylaxis						
None	Reference					
Yes	1.12 (0.93,1.35)	0.249	1.04 (0.92,1.17)	0.526	1.06 (0.96,1.17)	0.254
Chemical VTE thromboprophylaxis						
Yes	Reference					
None	0.94 (0.77,1.15)	0.577	0.97 (0.86,1.09)	0.618	0.96 (0.87,1.07)	0.475
Type of chemical VTE thromboprophylaxis:						
Aspirin						
No	Reference					
Yes	1.09 (0.96,1.25)	0.177	0.91 (0.84,0.99)	0.035	0.96 (0.90,1.03)	0.265
LMWH						
No	Reference					
Yes	1.02 (0.93,1.13)	0.619	1.05 (0.97,1.11)	0.131	1.04 (0.99,1.10)	0.122
Pentasaccaride						
No	Reference					
Yes	1.14 (0.76,1.71)	0.520	1.05 (0.81,1.36)	0.714	1.08 (0.87,1.34)	0.516
Warfarin						

	Revision for infection		Aseptic revision		All cause revision	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
No	Reference					
Yes	0.97 (0.59,1.58)	0.889	0.88 (0.64,1.20)	0.413	0.90 (0.69,1.18)	0.442
Direct Thrombin Inhibitor						
No	Reference					
Yes	1.01 (0.85,1.19)	0.941	0.92 (0.83,1.03)	0.133	0.95 (0.86,1.03)	0.218
Factor Xa inhibitor						
No	Reference					
Yes	0.83 (0.58,1.21)	0.334	0.40 (0.26,0.63)	<0.001	0.58 (0.44,0.77)	<0.001

CI – Confidence intervals
HR – Hazard ratio
ASA – American Society of Anesthesiologists
BMI – Body mass index
VTE – Venous thromboembolic
LMWH – Low molecular weight heparin

Table 5: Multivariable Multivariable (adjusted) analysis of association between revision rate (all cause) and the use ALBC, adjusting for other factors (including year of operation) using un-stratified and stratified Cox proportional hazard models. (Only variable categories with significant influences included here).

	UNSTRATIFIED ANALYSIS				**STRATIFIED ANALYSIS**			
	ALL PATIENTS		**EXCLUDING DEAD**		**ALL PATIENTS**		**EXCLUDING DEAD**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age								
<64	Reference							
64-71	0.61 (0.58,0.65)	<0.001	0.62 (0.59,0.66)	<0.001	0.61 (0.58,0.65)	<0.001	0.63 (0.59,0.66)	<0.001
71.1-77	0.48 (0.45,0.51)	<0.001	0.51 (0.48,0.55)	<0.001	0.48 (0.45,0.51)	<0.001	0.51 (0.48,0.55)	<0.001
>77.1	0.38 (0.35,0.41)	<0.001	0.45 (0.42,0.49)	<0.001	0.38().35,0.41)	<0.001	0.46 (0.42,0.50)	<0.001
Sex								
Female	Reference							
Male	1.19 (1.13,1.25)	<0.001	1.21 (1.16,1.27)	<0.001	1.19 (1.13,1.25)	<0.001	1.22 (1.16,1.28)	<0.001
ASA grade								
1	Reference							
2	1.01 (0.94,1.09)	0.753	1.02 (0.95,1.10)	0.608	1.02 (0.94,1.10)	0.688	1.03 (0.96,1.11)	0.427
≥3	1.20 (1.09,1.32)	<0.001	1.27 (1.16,1.40)	<0.001	1.21 (1.10,1.33)	<0.001	1.29 (1.17,1.42)	<0.001
BMI	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Indication								
Other	Reference							
Osteoarthritis	0.95 (0.83,1.10)	0.502	0.93 (0.81,1.07)	0.327	0.95 (0.83,1.10)	0.496	0.93 (0.81,1.08)	0.348
Cement type								
Plain	Reference							
Antibiotic loaded	0.75 (0.64,0.89)	0.001	0.73 (0.62,0.86)	<0.001	0.78 (0.67,0.92)	0.003	0.78 (0.66,0.92)	0.003
Cement viscosity								
High	Reference							
Medium	1.05 (0.93,1.18)	0.444	1.05 (0.94,1.18)	0.387	1.05 (0.94,1.18)	0.386	1.05 (0.94,1.18)	0.397
Low	1.29 (0.93,1.77)	0.122	1.37 (0.99,1.88)	0.057	1.25 (0.90,1.72)	0.178	1.241 (0.9,1.71)	0.187
Bearing								
Fixed	Reference							
Mobile	1.24 (1.13,1.36)	<0.001	1.26 (1.14,1.38)	<0.001	1.21 (1.10,1.32)	<0.001	1.20 (1.09,1.31)	<0.001
Unknown	0.57 (0.14,2.27)	0.422	0.56 (0.14,2.23)	0.407	0.56 (0.14,2.25)	0.413	0.53 (0.13,2.13)	0.371
Constraint								
Unconstrained	Reference							
Posterior stabilized	1.27 (1.20,1.34)	<0.001	1.28 (1.21,1.35)	<0.001	1.26 (1.19,1.33)	<0.001	2.01 (0.50,8.07)	<0.001
Other	1.91 (0.48,7.67)	0.360	1.98 (0.49,7.92)	0.336	1.91 (0.48,7.65)	0.363		0.324
P*atellar resurfaced*								
No	Reference							
Yes	0.77 (0.73,0.81)	<0.001	0.77 (0.73,0.81)	<0.001	0.78 (0.74,0.82)	<0.001	0.77 (0.74,0.82)	<0.001

CI – Confidence intervals
HR – Hazard ratio
BMI – Body mass index
ASA – American Society of Anesthesiologists